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Acta Clinica Belgica

International Journal of Clinical and Laboratory Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/yacb20

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To cite this article: Thomas Vanassche, Matthias M Engelen, Christelle Orlando, Kristel Vandenbosch, Alain Gadisseur, Cedric Hermans, Kristin Jochmans, Jean-Marc Minon, Serge Motte, Harlinde Peperstraete, Pierre Péters, Muriel Sprynger, Patrizio Lancellotti, Isabelle Dehaene, Patrick Emonts, Christophe Vandenbriele, Peter Verhamme & Cecile Oury (2023) The 2023 Belgian clinical guidance on anticoagulation management in hospitalized and ambulatory COVID-19 patients, Acta Clinica Belgica, 78:6, 497-508, DOI: 10.1080/17843286.2023.2241692

To link to this article: https://doi.org/10.1080/17843286.2023.2241692

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ACTA CLINICA BELGICA
2023, VOL. 78, NO. 6, 497–508
https://doi.org/10.1080/17843286.2023.2241692

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REVIEW

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The 2023 Belgian clinical guidance on anticoagulation management in hospitalized and ambulatory COVID-19 patients

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ABSTRACT

COVID-19 is associated with an increased risk for thrombotic complications. The trials investigating the optimal thromboprophylactic dose are performed in challenging times and seemingly produce conflicting evidence. The burdensome circumstances, divergent endpoints, and different analytical approaches hamper comparison and extrapolation of available evidence. Most importantly, clinicians should provide thromboprophylaxis in hospitalized COVID-19 patients while (re)assessing bleeding and thrombotic risk frequently. The COVID-19 Thromboprophylaxis Working Group of the BSTH updated its guidance document. It aims to summarize the available evidence critically and to guide clinicians in providing the best possible thromboprophylaxis.

ARTICLE HISTORY
Received 22 February 2023
Accepted 24 July 2023

KEYWORDS
Practice guideline; COVID-19; thrombosis; anticoagulants

Background

Coronavirus disease 2019 (COVID-19) continues to dominate global health. Early on, the disease was associated with a high incidence of incidental and symptomatic venous thromboembolism (VTE) in hospitalized patients even when receiving prophylactic doses of low molecular weight heparin (LMWH) [1–11]. In these patients, a thromboinflammatory response follows the initial phase of viral replication and markers of inflammation and hypercoagulation are associated with disease severity and outcome [12,13]. Consequently, intermediate or therapeutic doses LMWH were suggested to improve outcome in patients hospitalized with COVID-19 [12–17].

The Belgian Society on Thrombosis and Haemostasis (BSTH) produced a guidance document early 2020 to guide COVID-19 thromboprophylaxis in clinical practice [18]. In the meantime, many studies investigated the optimal dose of LMWH for in- and out-hospital thromboprophylaxis [19–49]. Therefore, an update of the 2020 guidance was needed.

It should be clear from the start that the available evidence mostly concerns unvaccinated patients infected with early Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) variants. Besides thromboprophylaxis, general care for patients with COVID-19 also vastly improved since the start of the first randomized trials. All this is seemingly demonstrated by the decreased incidence of thrombotic events in current COVID-19 patients and rather low event rates in most recent randomized trials [6,37]. Nevertheless, effective and safe thromboprophylaxis remains of uppermost importance to keep thrombotic complications minimal. The following recommendations will clarify that adequate COVID-19 thromboprophylaxis does not come in a 'one size fits all approach'.

Methods

The BSTH gathered the Belgian Working Group on COVID-19 thromboprophylaxis consisting of clinicians, experts, and clinical trialists to revisit the current guidance document and review the most

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/17843286.2023.2241692.

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Table 1. Summary of international recommendations.

Society	Year	Moderately (non-critically) ill	Critically ill	Post-discharge thromboprophylaxis
American Society of Hematology (ASH)	2022	Conditional recommendation of therapeutic over prophylactic intensity thromboprophylaxis with individualized assessment of thrombotic and bleeding risk. (very low certainty) [50]	Conditional recommendation of prophylactic over therapeutic intensity thromboprophylaxis (low certainty) [51]	Conditional recommendation against the use of outpatient anticoagulant prophylaxis [52]
CHEST	2022 2020*	Conditional recommendation of therapeutic over standard dose heparin thromboprophylaxis when low bleeding risk. When not therapeutic, prophylactic over intermediate-dosed thromboprophylaxis is strongly recommended. (Ungraded Consensus-Based Statement) [53]	Conditional recommendation of standard over intermediate or therapeutic dose heparin thromboprophylaxis. (Ungraded Consensus-Based Statement) [53]	Recommendation against the use of outpatient anticoagulant prophylaxis; should be considered when low risk of bleeding. * [54]
International Society on Thrombosis and Haemostasis (ISTH)	2022	Recommendation of prophylactic dose over no anticoagulation (I, B-R). Intermediate dose not recommended (III, B-R). When low bleeding risk with risk factors for thromboembolism or organ failure (e.g. elevated D-dimers or increased oxygen requirements), class I recommendation of therapeutic over intermediate or prophylactic dose (I, A) [55].	Therapeutic and intermediate dose thromboprophylaxis is not recommended over prophylactic dose (III, B-R) [55].	Class 2b consideration for post-discharge thromboprophylaxis with prophylactic dose rivaroxaban in selected patients for 30 days (2b, B-R) [55].
National Institutes of Health and Care Excellence (NICE)	2022	Recommendation for prophylactic dose LMWH in patients with any form of oxygen support without bleeding risk. Conditional recommendation for considering therapeutic dose LMWH with oxygen support without bleeding risk. Consensus recommendation for dose adjustment in patients with renal impairment and extreme body weights; reassesses bleeding risk and review VTE prophylaxis when clinical condition changes [56].	Recommendation for prophylactic dose LMWH in patients with any form of oxygen support without bleeding risk. Intermediate or therapeutic dose LMWH only in research setting [56].	In-hospital thromboprophylaxis should be continued for a minimum of 7 days, including after discharge [56].
National Institutes of Health (NIH)	2022	Recommendation for prophylactic dose LMWH (AIIb) and therapeutic dose LMWH when D-dimer levers above ULN, low-flow oxygen and without increased bleeding risk (CIIa) [57].	Recommendation for prophylactic dose LMWH (AI) and against intermediate or therapeutic dose anticoagulation except clinical trial (BI). When no VTE present, recommendation to switch a non-ICU patient with therapeutic dose to prophylactic dose once admitted to the ICU (BIII) [57].	Recommends against routinely continuing VTE prophylaxis after hospital discharge except in a clinical trial (AIII) [57].
World Health Organization (WHO)	2021	Conditional recommendation for prophylactic over intermediate or therapeutic dose anticoagulation. (very low certainty) [58]	Conditional recommendation for prophylactic over intermediate or therapeutic dose anticoagulation. (very low certainty) [58]	

recent evidence. As shown in Figure 2 and Table 1, the Working Group also compares its guidance with international guidelines. Where the first guidance document was mainly based on retrospective and often single-center small studies, the following guidelines were established after more randomized trials became available. Although large trials have been conducted, most trials were performed in times with a more pathogenic variant in unvaccinated patients with overburdened hospitals. Given the circumstances, all studies have their limitations and should be interpreted with great caution. It remains challenging to evaluate to which extent the results of these studies can be extrapolated to current clinical practice with less pathogenic variants in a largely vaccinated patient population.

Changes compared to 2020 recommendations

(1) Recommendations based on a large set of (randomized) trials.
(2) In hospitalized non-critically ill – that is ward – patients we recommend weight adjusted prophylactic-dosed LMWH. In a subgroup of patients with a low bleeding risk, AND D-dimer levels above the upper limit of normal, AND low-flow oxygen support, therapeutic-dosed LMWH might be considered.
(3) In hospitalized critically ill patients, we recommend weight adjusted prophylactic-dosed LMWH over therapeutic-dosed LMWH. The intermediate-dosed LMWH, recommended in the 2020 BSTH guidance is, however, still considered good clinical practice.

(4) Post-discharge thromboprophylaxis is recommended in high-risk patients only. In patients with an IMPROVEDD VTE score ≥ 4 at discharge or IMPROVE VTE sore of 2–3, without a high bleeding risk or dual anti-platelet therapy, and a creatinine clearance above 30 mL/min/1.73 m^2, we recommend prophylactic-dosed LMWH (50IU/kg) or low- dose rivaroxaban (10 mg; not reimbursed in Belgium) up to 6 weeks depending on the persistence of risk factor(s).

Recommendations – Figure 1

General considerations

This guidance document is divided into several parts focusing on outpatients, hospitalized non-critical ill patients, critically ill patients, and discharged patients. Lastly, there is a word on COVID-19 thromboprophylaxis in pregnancy. In each section, the following general considerations are essential.

Assess bleeding risk

We recommend to routinely and repeatedly assess bleeding risk when evaluating the most appropriate thromboprophylactic strategy. As apparent from Figure 1, each step should account for bleeding risk. When changing strategies or when patients deteriorate, bleeding risk should be reassessed. Fundamental criteria for bleeding risk include platelet count ($<50\times10^3$/µL), recent major bleeding, dialysis, frail elderly patients, or even low fibrinogen levels in selected randomized trials. The risks and benefits of thromboprophylaxis should be weighed on an individual basis.

Prior indication

We recommend continuation of anticoagulant treatment in patients with a prior indication for therapeutically dosed anticoagulation. In SARS-CoV-2 positive patients on oral anticoagulation without symptoms of COVID-19, oral treatment should be continued. In SARS-CoV-2 positive patients with symptoms of COVID-19 admitted to the hospital (for COVID-19), we recommend switching to equivalent dosages of LMWH. For patients in whom bioavailability of oral compounds cannot be guaranteed, we recommend switching to LMWH subcutaneously in an equivalent dose. With increased bleeding risk, especially in the critically ill, the dose should be reconsidered depending on the underlying disease (e.g. stroke prevention in atrial fibrillation vs. anticoagulation regimen in mechanical heart valves).

High suspicion for venous thromboembolism, no systematic screening

We do not recommend systematically screening for VTE in all COVID-19 patients. However, there should be an increased awareness of VTE during hospitalization: look for clinical signs like swollen leg, hypoxemia non-proportionate to the respiratory status, acute right ventricle failure or dilation, and catheter issues. Reassess diagnostic clues when patients deteriorate. We advise a low threshold to perform imaging whenever VTE is suspected. When strongly suspected, consider therapeutic anticoagulation in patients without upfront contra-indications, especially in the intensive care unit (ICU) when it is not always possible to immediately confirm clinical suspicion by imaging.

New or proven venous thromboembolism

We recommend therapeutic-dosed LMWH in COVID-19 patients with a new VTE diagnosis as long as COVID-19 symptoms are present. We advise switching to oral anticoagulation conform traditional guidelines in treating VTE after resolution of COVID-19 symptoms and when bioavailability can be guaranteed. In patients with oral anticoagulation because of a recent VTE, continue therapeutic-dosed anticoagulation and switch to an equivalent LMWH dose in case of symptomatic COVID-19 or when bioavailability cannot be guaranteed.

Non-hospitalized patients

In outpatients with COVID-19 not previously hospitalized for COVID-19, we do not routinely recommend initiation of anticoagulation therapy. In patients already treated with anticoagulation, treatment should be continued as before with attention for bioavailability of oral drugs. Nevertheless, we advise a high vigilance for thrombotic complications and developing needs for hospitalization.

Hospitalized patients – non-critically ill

In non-critically ill patients hospitalized with COVID-19 without known VTE or prior indication for anticoagulation, we advise a weight-adjusted prophylactic LMWH (50IU/kg once daily with creatinine clearance (CrCl) >15 mL/min/1.73 m2). We conditionally consider (very low certainty) therapeutic-dosed LMWH in patients without bleeding risk, with D-dimer levels above the upper limit of normal (ULN) at admission, and with supplementary low-flow oxygen; i.e. 100IU/kg twice daily with CrCl >30 mL/min/1.73 m2 and 100IU/kg once daily with CrCl 15–30 mL/min/1.73 m2. When patients need advanced care with transfer to the ICU, reconsider the risk-benefit of the current strategy. In patients with high thrombotic risk and low bleeding risk, intensified dosages up to an intermediate-dosed LMWH could still be considered in ICU patients (cfr.

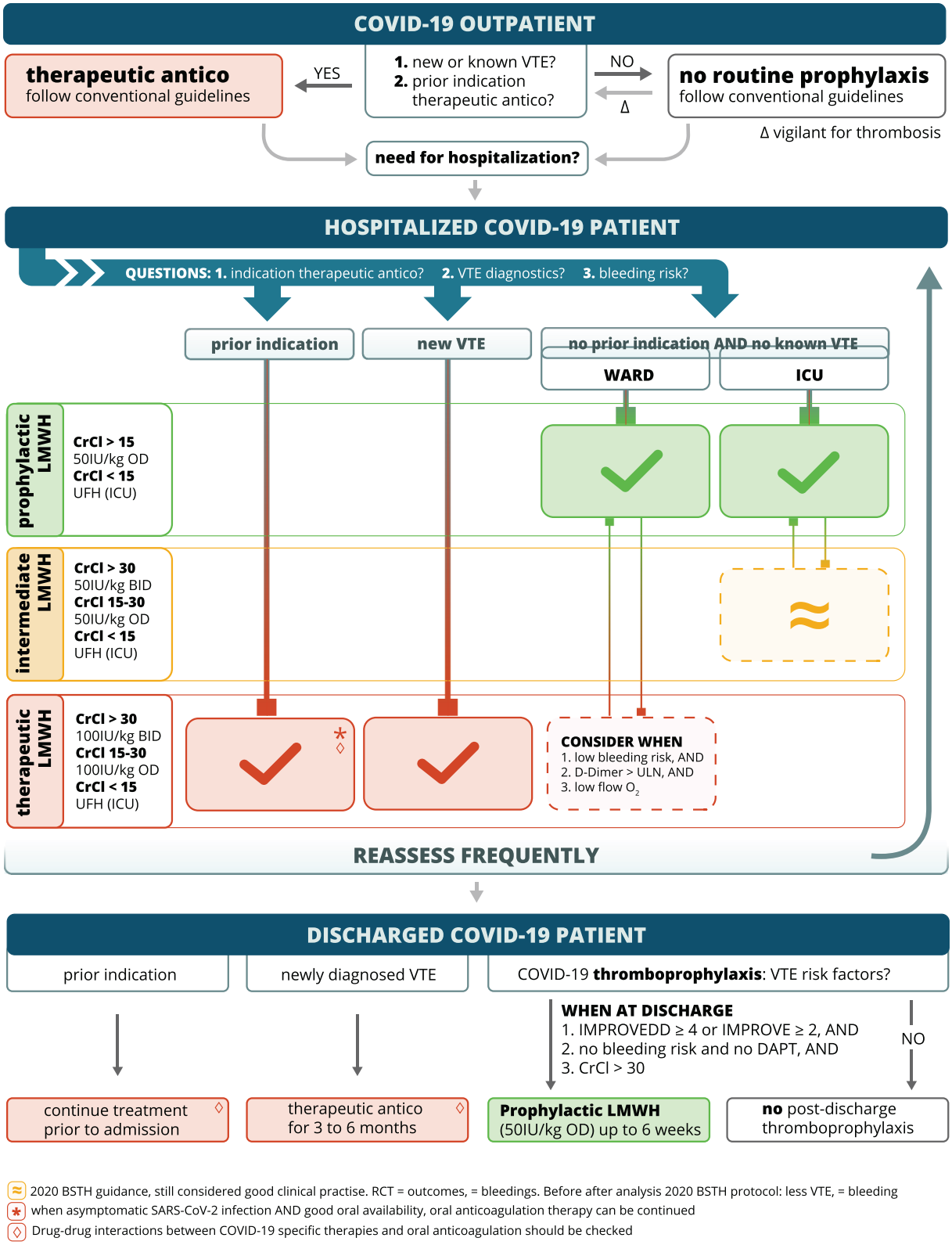


Figure 1. BSTH recommendations on COVID-19 thromboprophylaxis. Flowchart of the 2023 BSTH recommendations. In hospitalized patients, different settings require different dosages of anticoagulation. Dose intensities are shown as rows and the different patient profiles are shown in columns. The checkmarks represent the general recommendations. The orange dashed box (≈) represents previous guidance, still considered good clinical practice. The asterisk (*) notes that in asymptomatic SARS-CoV-2 positive patients with good oral availability, oral anticoagulation can be continued. The diamond (◊) warns to check for possible drug–drug interactions between COVID-19 specific therapies and oral anticoagulant drugs. Venous thromboembolism, VTE; therapeutic dose anticoagulation, low molecular weight heparin, LMWH; creatinine clearance in mL/min/1.73 m^2, CrCl; twice daily, BID; once daily, OD; intensive care unit, ICU; upper limit of normal, ULN; unfractionated heparin, UFH; dual antiplatelet therapy, DAPT

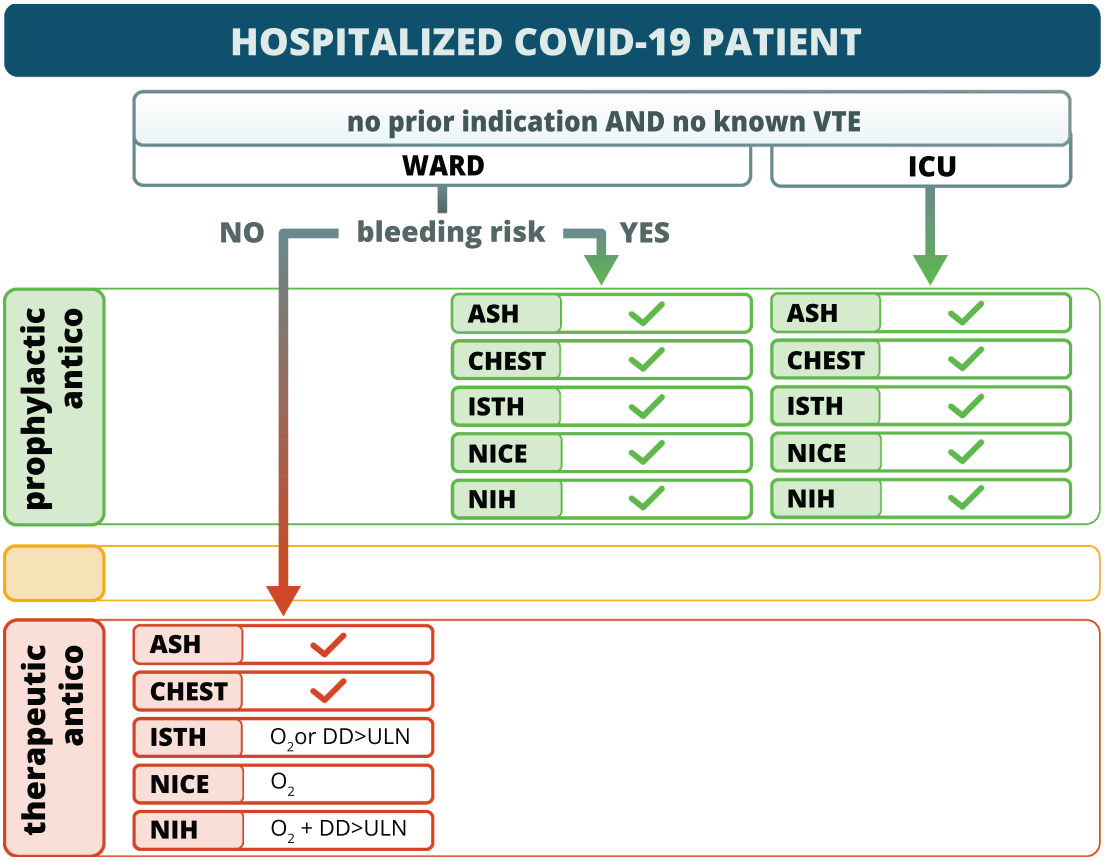


Figure 2. Summary of international recommendations. Overview of (conditional) recommendations. Dose intensities are shown as rows and the different patient profiles are shown in columns. The checkmarks represent the general recommendations. In the non-critically ill, the international societies recommend therapeutic anticoagulation in patients without bleeding risk. ISTH, NICE and NIH add additional criteria before recommending therapeutic over prophylactic anticoagulation. In patients with increased bleeding risk and in the critically ill patients, all societies recommend prophylactic anticoagulation. References and more details are provided in Table 1. Fundamental criteria for bleeding risk include – but are not limited to – platelet count ($<50\times10^3$/μL), recent major bleeding, dialysis, frail elderly patients, or low fibrinogen levels. American Society of Hematology, ASH; International Society on Thrombosis and Haemostasis, ISTH; National Institutes of Health and Care Excellence, NICE; National Institutes of Health, NIH; supplementary low flow oxygen, O_2; D-dimer levels above upper limit of normal, DD>ULN.

'Hospitalized patients – critically ill'). If these criteria are not met, dose reduction to prophylactic-dosed LMWH is recommended. When patients deteriorate, VTE diagnostics and (major) bleeding risk must be re-evaluated

Hospitalized patients – critically ill

In critically ill patients hospitalized with COVID-19 without known VTE or prior indication for anticoagulation, we conditionally recommend (with low certainty) prophylactic-dosed LMWH in the ICU population. This is 50IU/kg once daily when CrCl >15 mL/min/1.73 m2. When CrCl <15 mL/min/1.73 m2, unfractionated heparin (UFH) is recommended. In patients with high thrombotic risk and low bleeding risk, intensified dosages up to intermediate-dosed LMWH could be considered. Most importantly, with clinical deterioration, patients should be reassessed for thrombotic complications and bleeding risk; that includes ward patients transferred to ICU. If selected ward patients on therapeutic-dosed LMWH are transferred to the ICU, and there is no clear conventional indication for therapeutic dosages, we recommend reducing to a prophylactic (or intermediate) dose of LMWH.

The previous BSTH guidelines suggested intermediate but not therapeutic dosing in the critically ill (50IU/kg anti-Xa LMWH twice daily). Trials investigating intermediate-dosed LMWH over prophylactic-dosed LMWH are scarce and mostly underpowered to show benefit, but do not show signs of harm like (major) bleeding as stated below. Even with rigorous patient selection, the use of therapeutic-dosed LMWH in the ICU is associated with increased non-fatal bleeding rates. Based on observational data gathered in a Belgian tertiary center, we still consider this weight-adjusted intermediate dosing in the critically ill as good clinical practice [33]. So, essentially, if an ICU patient with a high thrombotic risk but relatively low bleeding risk, is believed to benefit from a slightly higher than prophylactic-dosed LMWH, we recommend intermediate-dosed LMWH over therapeutic-dosed LMWH. We agreed that it would still be of added value to clinical

practice to see well-designed randomized clinical trials comparing intermediate-dosed LMWH with prophylactic- dosed LMWH, with the current SARS-CoV-2 variants and optimized COVID-19 care.

Available evidence, summarized below (also see Supplementary Table S1), is conflicting and should be interpreted with great care. It seems that different patient groups could benefit from different strategies. Most importantly, whatever strategy is used, there should be great focus on (re)evaluation of thrombotic and bleeding risk with adequate treatment adjustment when needed.

Hospitalized patients – thromboprophylaxis at discharge

We recommend evaluating the need for anticoagulation after discharge routinely. In patients with a prior indication for anticoagulation, we recommend switching back to the initial anticoagulation strategies. When switching back, clinicians should take into account the (CYP) interactions of oral anticoagulants with the antiviral and anti-inflammatory drugs used to treat COVID-19 patients as the pharmacodynamics and -kinetics of oral anticoagulants could be altered. In patients who developed VTE during hospitalization, therapeutic anticoagulation (tAC) should be continued for 3–6 months as per standard of care. Consider using therapeutic-dosed LMWH as long as COVID-19 symptoms are present with out-patient follow-up to decide on oral anticoagulation and long-term strategies. We do not recommend post-discharge thromboprophylaxis in all patients. However, in patients with an IMPROVEDD VTE score ≥ 4 at discharge or IMPROVE VTE sore of 2–3, without a high bleeding risk or DAPT, and a CrCl >30 mL/min/1.73 m2, we conditionally recommend prophylactic-dosed LMWH (50IU/kg) or low-dose rivaroxaban (10 mg; not reimbursed in Belgium) up to 6 weeks depending on the persistence of risk factor(s).

Pregnancy

In pregnant women with confirmed COVID-19 but without severe symptoms, we recommend against thromboprophylaxis if not otherwise indicated. In pregnant women with severe symptoms (e.g. high fever, immobilisation), we recommend thromboprophylaxis. For hospitalized, asymptomatic COVID-19 positive pregnant women, we recommend a standard obstetric thromboprophylactic risk assessment, based on current recommendations [59]. This assessment should be repeated if necessary. For hospitalized, symptomatic COVID-19 positive pregnant women, we recommend starting thromboprophylaxis (unless contraindicated). If VTE is confirmed during the 6 months of pregnancy, we recommend continuing therapeutic-dosed LMWH for 3 to 6 months with afterwards a switch to a prophylactic-dosed LMWH until 6 to 8 weeks post-partum. When VTE is diagnosed in the last trimester, it's recommended to minimize interruption of the therapeutic dose before and after delivery (cave-induced delivery). In this case, therapeutic-dosed LMWH should be continued up until 6 to 8 weeks post-partum, with a total treatment time of minimal 3 months, because of the increased VTE risk during the post-partum period [61]. We recommend VTE prophylaxis in postpartum women with COVID-19, based on individual risk assessment. In the absence of risk factors requiring antepartum prophylaxis, we do not recommend postpartum prophylaxis in asymptomatic or mildly symptomatic patients with uncomplicated delivery and no obstetric indication for postpartum VTE prophylaxis. If antepartum prophylaxis was given because of COVID-19, we recommend continuing prophylaxis for at least 14 days. After 14 days, the need for anticoagulation should be reassessed according to risk–benefit balance (severity of COVID infection and other risk factors).

Understanding the available evidence

Non-hospitalized patients

Three randomized trials show comparable results for symptomatic patients with COVID-19 without need for hospitalization. The ACTIV-4B trial (NaN Invalid Date NaN - NaN Invalid Date NaN) included a total of 657 patients in four study arms; low dose aspirin, low dose apixaban (2×2.5 mg), therapeutic dose apixaban (2×5 mg), and placebo [19]. The primary endpoint was the composite of symptomatic VTE, arterial thromboembolism, myocardial infarction, ischemic stroke, hospitalization for cardiovascular or pulmonary events, and all-cause mortality for up to 45 days after treatment initiation. After recruiting 9% of the target number of patients, the study was stopped prematurely because the event rate was lower than expected. None of the three interventions showed a reduction of the primary endpoint. Only high-dose apixaban showed a significant higher (any) bleeding rate. The OVID study (15 August 2020 - 14 January 2022) included 472 patients to compare 14 days of enoxaparin 40 mg once daily to standard of care in outpatients [20]. There was no difference in the primary outcome of a composite of any unexpected hospitalization and all-cause death within 30 days. This study was also terminated early based on very low probability of showing superiority. Similarly, the ETHIC study (27 October 2020 - 8 November 2021) compares enoxaparin 40 mg once or twice daily based on body weight for 21 days with standard of care [21]. This study confirmed that there was no difference in the

composite of all-cause hospitalization and all-cause mortality at 21 days but was also terminated early due to slow enrolment and a lower-than-expected event rate. The baseline event rate in all these studies was overestimated at the time of power calculations during the first months of the pandemic with no vaccines available and underestimation of SARS-CoV-2 infections due to low test capacity at the time.

Hospitalized patients – non-critically ill

These recommendations changed over the last BSTH statement as new evidence emerged. Most important observational and randomized clinical trials are summarized in the supplementary tables . These trials are of high value, but all have limitations and must be interpreted carefully. Observational trials showed overall benefit for LMWH over no heparin in COVID-19 patients [22–29]. There is some observational evidence positioning intermediate- dosed LMWH as the better option over prophylactic-dosed LMWH in a population with ward patients and a population with mixed ward-ICU patients [30,31]. Another observational trial could not confirm these results [32]. The previous BSTH guidelines also showed encouraging results in an observational cohort early in the pandemic [33]. Randomized trials tend to provide higher quality evidence, but still need to be carefully analyzed and put into perspective, especially with the challenges posed by a pandemic. Three RCT investigated therapeutic-dosed LMWH against local practice, all with a slightly different approach. The RAPID trial (29 May 2020 - 12 April 2021) included 465 moderately ill patients with elevated D-dimers (> ULN) and compared therapeutic-dosed LMWH with BMI-adjusted prophylactic-dosed LMWH [34]. The primary endpoint was the composite of death, invasive mechanical ventilation, non-invasive mechanical ventilation, or admission to an intensive care unit at 28 days. Therapeutic-dosed LMWH did not significantly reduce the composite primary endpoint, but there was a reduction in all-cause mortality (1.8 vs. 7.6%, ARR 5.8%). Importantly, this open-label study was underpowered for the primary composite endpoint and the secondary outcome of all-cause mortality, and the authors could not exclude performance bias. The HEP-COVID trial (8 May 2020 - 14 May 2021) included 253 patients with elevated D-dimers (≥4 ULN) or sepsis-induced coagulopathy score ≥ 4 to compare therapeutic-dosed LMWH with institutional LMWH (prophylactic- or intermediate LMWH or UFH) [35]. The primary endpoint was the composite of VTE, arterial thromboembolism, or death at 30 days. Therapeutic-dosed LMWH reduced the composite endpoint compared to *p*- or intermediate-dosed LMWH in non-ICU patients with D-dimers ≥4 ULN (n = 170). After analysis of the individual endpoints, only symptomatic deep vein thrombosis (DVT) was significantly lower in the non-ICU intervention group. This difference was not observed in ICU patients (n = 83). Notably, with the predefined inclusion criteria, the investigators target high-risk ward patients who might as well be hospitalized in ICU depending on center and circumstances, as ICU beds were limited early in the pandemic. In a Belgian observation trial during the same period (and SARS-CoV-2 variants), only 14% of ward patients met the D-dimer criteria (this is overestimated as D-dimers were collected within three days of admission) [33]. The multiplatform RCT (ATTACC, ACTIV-4a, and REMAP-CAP; 21 April 2020 - 22 January 2021) included 2219 moderately ill COVID-19 patients to compare therapeutic-dosed LMWH with institutional LMWH (open-label *p*- or intermediate-dosed LMWH) [36]. The primary endpoint was organ support-free days. The authors concluded that an initial strategy with therapeutic-dosed LMWH increased the probability of survival to hospital discharge with reduced use of organ support compared to usual care thromboprophylaxis. Mortality was 7.3 vs. 8.2% in interventions vs. usual care. Per protocol, the investigators stratified patients by D-dimer levels (>2 ULN, < 2 ULN, and unknown), but only the overall group showed a significant odds ratio with a high probability of superiority. Odds ratio in both high, low, and unknown D-dimer groups ranged from 1.2 to 1.3 in favor of therapeutic-dosed LMWH. However, despite a high probability of superiority, all odds ratios were non-significant based on 95% confidence intervals. Adherence to therapeutic-dosed LMWH in the intervention group was 79.6%; adherence to prophylactic-dosed LMWH was 71.7% in the usual care group. This adherence might be overestimated as protocol adherence was defined according to the anticoagulant dose equivalent administered within the first 24 to 48 h after randomization. A meta-analysis has been published based on these three studies [37]. Concerning intermediate-dosed LMWH, The X-COVID-19 randomized trial compared a fixed dose of intermediate-dosed LMWH with a fixed dose of prophylactic-dosed LMWH in 183 patients admitted to the medical ward [38]. The primary endpoint was the incidence of VTE (a composite of asymptomatic or symptomatic proximal DVT diagnosed by serial ultrasound screening, and symptomatic PE diagnosed by CTA). There was a reduction in VTE in patients receiving fixed-dose intermediate-dosed LMWH compared to fixed-dose prophylactic-dosed LMWH. However, this study was terminated early due to slow recruitment and, therefore, underpowered.

There are some general perspectives on the trials mentioned above. All trials took place during the first two waves of the global pandemic, meaning that there was a growing number of therapeutical advances and patients were infected with the first variants (Alpha, Beta, Delta, and Gamma) but not current, less

pathogenic variants. Additionally, most participants in the trials above were not vaccinated. All randomized trials excluded patients with additional risk for VTE or major bleeding, with study teams providing continuous support. If one makes a patient selection based on D-dimers, be aware that the randomized trials above stratified according to D-dimers at admission. Therefore, D-dimers rising throughout admission is not a 'validated' criterium to adjust thromboprophylaxis. Vigilance for VTE with rising D-dimers stays important, however.

International guidelines

As summarized in Figure 2 and Table 1, societies worldwide updated their COVID-19 thromboprophylaxis guidelines. Overall, there is consensus about the lack of robust, good-quality evidence. Nevertheless, all provide conditional recommendations regarding tAC in non-critically ill patients without bleeding risk. ASH and CHEST do not specify additional criteria, while ISTH (organ failure, increased oxygen support, or elevated D-dimers), NICE (low-flow oxygen support), and NIH (low-flow oxygen and D-dimers) do narrow down in varying degree the non-critically ill population eligible for tAC. For patients not on tAC, pAC is recommended. Only NICE shares a consensus recommendation for dose adjustment in patients with renal impairment and extreme body weights. WHO recommendations were not updated after the impactful randomized trials were published.

Hospitalized patients – critically ill

Thromboprophylaxis in critically ill medical patients with prophylactic-dosed LMWH is well established in clinical practice [39,40]. The above-mentioned recommendations focus on COVID-19 patients, based on emerging evidence from observational and randomized clinical trials, summarized in the supplementary tables. Randomized data is available for both therapeutic-dosed LMWH and intermediate-dosed LMWH compared to usual care thromboprophylaxis in the critically ill. The HEP-COVID trial (8 May 2020 - 14 May 2021) included 83 ICU patients with D-dimer levels ≥ 4 ULN or sepsis-induced coagulopathy score ≥ 4, comparing therapeutic-dosed LMWH with institutional LMWH (*p*- or intermediate-dosed LMWH or UFH) [35]. The primary endpoint was the composite of VTE, arterial thromboembolism, or death at 30 days. Therapeutic-dosed LMWH did not reduce composite endpoint compared to *p*- or intermediate- dosed LMWH. Overall mortality was 19 vs. 25% in ward and ICU patients combined. There were four major bleedings (8.9%) in the ICU stratum with therapeutic-dosed LMWH and none in the *p*- or intermediate-dosed LMWH group. The study has little power for the ICU stratum. Second, the multiplatform RCT (ATTACC, ACTIV-4a, and REMAP-CAP; 21 April 2020 - 19 December 2020) included 1098 critically ill patients to compare therapeutic-dosed LMWH with institutional LWMH (*p*- or intermediate-dosed LMWH) [41]. The primary endpoint was organ support-free days. Initial therapeutic-dosed LMWH did not show a higher probability of survival to hospital discharge or a higher number of days free of cardiovascular or respiratory organ support than *p*- or intermediate-dosed LMWH. Mortality was 37 and 35% in both groups. Due to the high probability of futility, inclusion was halted. Despite non-significant odds ratio confidence intervals, there was a relatively high probability of inferiority for therapeutic-dosed LMWH. The odds ratio for major bleeding in therapeutic-dosed LMWH was 1.5, but not statistically significant (3.8 vs. 2.3%). Adherence at day one after randomization in therapeutic-dosed LMWH was 78%, and in the institutional LMWH group 53.5% of patients received intermediate-dosed LMWH and 40.4% prophylactic-dosed LMWH. Putting these two RCTs into perspective, we can conclude that there is no added benefit for therapeutic-dosed LMWH in the critically ill and even some signs of inferiority and risk for major bleeding in a population with high mortality at the beginning of the pandemic. There is possibly no added benefit beyond *p*- to intermediate-dosed LMWH (78% therapeutic-dosed LMWH vs. 93.9% *p*- to intermediate-dosed LMWH in multiplatform RCT). However, most recently, the COVID-PACT trial (5 August – 2 March 2022) showed a reduction of thrombotic complications using therapeutic-dosed LMWH in an on-treatment analysis of 382 patients [42]. This at an expense of increased non-fatal bleeding rate, mainly driven by transfusion need (GUSTO moderate bleeding). The composite endpoint seems to be mainly driven by VTE, and there was no difference in all-cause mortality. Importantly, a predefined on-treatment analysis was used, compared to the intention to treat analysis in the other trials; the intention-to-treat analysis showed no significant difference in primary endpoint.

Two RCTs analyzed the potential benefit of intermediate-dosed LMWH over prophylactic-dosed LMWH. The INSPIRATION trial (29 July 2020 - 19 November 2020) included 562 patients in an open-label study with a primary endpoint defined as a composite of adjudicated venous or arterial thrombosis, ECMO, or all-cause death [43,44]. Intermediate-dosed LMWH did not reduce this endpoint compared with prophylactic-dosed LMWH at 30- and 90-day follow-up. There was no statistical difference in major bleeding. The study included critically ill ICU patients, with a mortality of 43–41%. On the other hand, the median ICU stay was only 5–6 days. Perepu et al. (26 April 2020, - 6 January 2021) compared all-cause mortality in a weight-adjusted intermediate-dosed LMWH with prophylactic-dosed LMWH in 176 patients admitted to the ICU

and-or ISTH overt DIC score ≥ 3 [45]. Ultimately, only 62% were admitted to ICU, and 23% needed mechanical ventilation. Despite no statistical difference in the primary endpoint of all-cause mortality (15 vs. 21%, HR 0.57, CI 0.28–1.17), the survival plot shows diverging curves. This study was underpowered, however, as the actual mortality was half of the estimates in the power calculation. Major bleeding was low (2%) in both groups. In these two trials, there is no sign of potential harm with intermediate-dosed LMWH. INSPIRATION showed no benefit with intermediate-dosed LMWH in a population with high mortality, Perepu et al. showed signs of benefit in a population with lower mortality (partially due to inclusion criteria and definition of critically ill patients), but the study was underpowered.

Some general considerations also apply to the RCTs focused on the critically ill. As with the ward population, all trials were performed during the first two waves of the global pandemic investigating early variants, accompanied by high mortality in unvaccinated patients, but also by a growing number of therapeutical advances. All randomized trials excluded patients with additional risk factors for VTE, or patients with an increased risk for, or a history of, major bleeding.

International guidelines

As summarized in Figure 2 and Table 1, societies worldwide updated their COVID-19 thromboprophylaxis guidelines. Overall, there is consensus about the lack of robust, good-quality evidence. Nevertheless, all provide conditional recommendations for prophylactic-dosed LMWH over therapeutic-dosed LMWH. CHEST, ISHT and NIH also recommend prophylactic-dosed LMWH over intermediate-dosed LMWH; while NICE only recommends intermediate-dosed LMWH or therapeutic-dosed LMWH in clinical research setting. WHO recommendations were not updated after the impactful randomized trials that were published. Notably, these recommendations were formed before the results of the COVID-PACT trial [42].

Hospitalized patients – thromboprophylaxis at discharge

Before the pandemic, the MARINER trial focused on post-discharge thromboprophylaxis of medically ill patients [46]. This multicenter-randomized clinical trial (7 January 2014 – 3 May 2018, $n = 4913$) compared rivaroxaban 10 mg for 45 days post-discharge to no post-discharge thromboprophylaxis in medically ill (non-COVID) patients with IMPROVEDD VTE score ≥ 4 or IMPROVE VTE of 2–3 at discharge. The primary endpoint was a composite of symptomatic VTE (DVT and nonfatal PE), myocardial infarction, non-hemorrhagic stroke, and cardiovascular death. The strategy resulted in a 28% reduction in fatal and major thromboembolic events (HR: 0.72; 95% CI: 0.52 to 1.00; $p = 0.049$) without significantly increasing major bleeding. Based on the same study principles, the MICHELLE trial (8 October 2020 – 29 June 2021, $n = 320$) compared rivaroxaban 10 mg to no post-discharge thromboprophylaxis in COVID-19 patients with IMPROVEDD VTE score ≥ 4 or IMPROVE VTE 2–3 at discharge [47]. The primary endpoint was a composite of VTE, screening detected (ultrasound or CT pulmonary angiogram) VTE, symptomatic arterial thrombotic events, and cardiovascular death. The trial excluded patients with active cancer or gastrointestinal ulcer, bronchiectasis, recent bleeding (<3 months) or surgery, dual antiplatelet therapy, or CrCl <30 mL/min. The intervention significantly improved outcomes (RR 0.33, 95% CI 0.12 to 0.90; $p = 0.0293$) without inducing major bleeding.

An observational trial (1 March 2020 - 31 May 2020, $n = 4906$) showed that advanced age >75 years, cardiovascular risk factors (personal history of VTE, coronary artery disease, carotid occlusive disease, and peripheral arterial disease), chronic kidney disease, IMPROVEDD ≥ 4, and ICU stay were associated with major post-discharge thromboembolic events and death [48]. Post-discharge thromboprophylaxis was recommended in patients with IMPROVEDD ≥ 4 or D-dimer twice the upper limit of normal (ULN) and was associated with a reduction in the composite of VTE, arterial thrombotic events, and all-cause mortality in a sensitivity analysis (OR, 0.55; 95% CI, 0.37–0.83; P 0.0046). Following the first BSTH guidance, an observational study in a tertiary care center routinely screened COVID-19 patients 6 weeks after hospital discharge [49]. With adequate in-hospital thromboprophylaxis (weight-and severity adjusted LMWH), selectively providing post-discharge thromboprophylaxis (median 14 days) in high-risk patients seems safe with no major bleeding, and potentially effective.

Several reports warn for the use of oral anticoagulants in combination with COVID-19 associated drugs such as antivirals and anti-inflammatory drugs as they might influence pharmacodynamics and kinetics [60,61]. Depending on (CYP) metabolization and interaction profiles, the anticoagulant action might be decreased or increased, resulting in an increased thrombotic or bleeding risk. It is therefore advisory to check interactions between the oral anticoagulant drugs and the drugs used in hospital to treat the COVID-19 patient, and how long the metabolic effects last, before blindly switching back to the oral compound. In other words, some patients might benefit to continue LMWH for several days at home before switching back to the oral anticoagulant.

International guidelines

In general, there is a conditional recommendation against routine post-discharge thromboprophylaxis in COVID-19 patients. CHEST and ISTH consider post-discharge thromboprophylaxis in a subgroup of patients.

NICE recommends an in-hospital thromboprophylaxis for at least 7 days, with continuation of pAC after discharge if needed to meet this treatment period.

Conclusion

COVID-19 is associated with an increased risk for thrombotic complications. The trials investigating the optimal thromboprophylactic dose are performed in challenging times and seemingly produce conflicting evidence. The burdensome circumstances, divergent endpoints, and different analytical approaches hamper comparison and extrapolation of available evidence. Most importantly, clinicians should provide thromboprophylaxis in hospitalized COVID-19 patients while (re)assessing bleeding and thrombotic risk frequently. The COVID-19 Thromboprophylaxis Working Group of the BSTH updated its guidance document to summarize the available evidence critically and to guide clinicians in providing the best possible thromboprophylaxis.

Abbreviations

BSTH	Belgian Society on Thrombosis and Haemostasis
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
COVID-19	coronavirus disease 2019
VTE	venous tromboembolism
DVT	deep vein thrombosis
LMWH	low molecular weight heparin
ICU	intensive care unit
CrCl	creatinine clearance (in mL/min/1.73 m^2)

Disclosure statement

No potential conflict of interest was reported by the author (s).

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